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Letter to the Editor

Intensive Immunosuppression Therapy for Aplastic Anemia Associated with Dyskeratosis Congenita

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Comoli et al recently described a patient with dyskeratosis congenita (DC) whose bone marrow failure (BMF) appeared to improve following a brief course of antilymphocyte globulin and cyclosporine A [1]. He was reported to have sustained bone marrow remission for 6 months. This is the first report to suggest that severe aplastic anemia in a patient with DC might respond to immunosuppressive therapy (IST); consequently, it raises important considerations.

The patient's phenotype is certainly consistent with DC (the diagnostic triad: dystrophic nails, reticulated skin pigmentation, and oral leukoplakia, associated with BMF) [2]. However, in this era of molecular diagnoses, it would be useful to know whether the patient had a germline mutation in any of the genes associated with DC, eg, *DKC1* or *TERC* (or even *TERT*) [3], and/or whether his telomeres were short [4].

To further assess whether IST might be appropriate treatment in a well-characterized set of patients with DC, we reviewed the experience of our own DC cohort, which is a subset of patients from the National Cancer Institute (NCI) Inherited Bone Marrow Failure Syndromes Study (www.marrowfailure.cancer.gov). There were 36 affected individuals among 16 DC families in this cohort, including 1 family with affected individuals in 3 generations (Table 1). Sixteen patients were seen by the study team, 14 were deceased family members with medical records of variable degrees of completeness, and 6 were patients with good medical records who were not yet seen by the study team.

There was an excess of males in the total cohort, and in those with BMF. The 5 patients who were treated with IST did not differ from the other subjects in age at BMF, age at diagnosis of DC, or interval from the diagnosis of BMF to the diagnosis of DC. The diagnosis of DC in the NCI cohort included 2 of the 3 components of the diagnostic triad in 21 of the 31 subjects in which adequate data were available, and in 4 of the 5 individuals who received IST (no significant difference). Ten of the DC patients had cancer (primarily tongue squamous cell carcinoma), which preceded the diagnosis of DC in 8. All 21 living DC patients had short telomeres in their white cells as indicated by flow fluorescence in situ hybridization analysis [5], and 10 had deleterious mutations in *DKC1* or *TERC*.

Five patients in the NCI DC cohort received immunosuppressive therapy prior to enrollment in the NCI study. Four were treated with antithymocyte globulin plus cyclosporine, and 1 received cyclosporine alone. None had sustained responses to the IST. Although the number of patients treated with DC in our cohort was small, the absence of any objective response is statistically significant when compared with the expected response rate of 50% to 90% in patients with acquired aplastic anemia ($P = .03$, 1-sided binomial probability test) [6].

It should be pointed out that the rapid response in the patient reported by Comoli et al [1] is quite unusual in patients with acquired aplastic anemia [7]. Despite the temporal association of the IST with hematologic improvement, we might speculate that the response was related to treatment-independent fluctuation in the degree of hematopoietic failure, which is sometimes seen in patients with inherited BMF syndromes [8].

It is generally thought that patients with any of the inherited BMF syndromes do not respond to IST. There are other medical modalities that have been used with some success for treatment of BMF in patients with DC, such as androgens or erythropoietin plus granulocyte colony-stimulating factor [9]. Survival following hematopoietic stem cell transplantation has been approximately 25% in the past [8], although recent short-term successes have led to its being considered a legitimate treatment option in this setting [10]. IST might be considered for those patients for whom there is not an

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Table 1.
National Cancer Institute Dyskeratosis Congenita (DC) Patients*

	Total Cohort	Subjects without BMF	Subjects with BMF	Subjects with IST
Number of subjects	36	6	30	5
Male:Female, n	25:11	5:1	20:10	2:3
Median age at BMF, y (range)	18 (0-60)	—	18 (0-60)	5.1 (0.8-28)
Median age at diagnosis of DC, y (range)	19 (0-47)	25 (14-26)	15 (0-47)	5 (1-43)
Median interval from BMF to diagnosis of DC, y (range)	1 (–1-23)	—	1 (–1-23)	2 (0-23)†
Number with 2 of 3 in diagnostic triad‡ (%)	21 (58)	1 (17)	16 (53)	4 (80)
Number with mutations in *DKC1*, *TERC*, or *TERT*	11	0	10	1
Number with short telomeres§	21	2	19	5

*BMF indicates bone marrow failure; IST, immunosuppressive therapy.
†Actual intervals 0, 0.4, 2, 3, and 23 years.
‡Dyskeratotic nails, reticular pigmentation, or leukoplakia.
§15 were deceased and thus did not have telomere length examined.

appropriate stem cell donor, or who do not accept the risk of transplantation. We agree with Comoli et al that IST should be examined in the context of a controlled trial, and we suggest comparing IST with androgens or growth factors, because the latter modalities have shown significant therapeutic activity [7]. The use of IST in patients with DC should be considered investigational at this time.

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